Reprinted from CLINICAL PHARMACOLOGY AND THERAPEUTICS, St. Louis
Vol. 64, No. 5, pp. 562-568, November, 1998 (Printed in the U.S.A.)

The substance P receptor antagonist CP-99,994 reduces acute postoperative pain

Background: Animal studies suggest that substance P, a peptide that preferentially activates the neurokinin-1 (NK_1) receptor, is involved in pain transmission, with particular importance in pain after inflammation.
Methods: The analgesic efficacy of CP-99,994, a NK_1 receptor antagonist, was compared with ibuprofen and placebo in 78 subjects undergoing third molar extraction. The initial 60 subjects randomly received 1 of 3 possible treatments in a double-blind fashion before oral surgery: 750 μg/kg CP-99,994 infused intravenously over 5 hours on a tapering regimen starting 2 hours before surgery, 600 mg oral ibuprofen 30 minutes before surgery, or placebo. In a second study, 18 subjects were randomized to the same regimens starting 30 minutes before surgery to maximize the amount of CP-99,994 circulating during pain onset.
Results: In the first study, ibuprofen significantly reduced pain, as measured by visual analog scale, from 90 to 240 minutes postoperatively compared with placebo. CP-99,994 produced analgesia that was significant at 90 minutes ($P < 0.01$ compared with placebo), but not at subsequent time points. In the second study, ibuprofen and, to a lesser extent, CP-99,994 significantly suppressed pain in comparison to placebo at 60, 90, and 120 minutes ($P < 0.05$). The incidence of side effects was similar across groups.
Conclusions: This replicate demonstration that a NK_1 receptor blocker relieves clinical pain supports the hypothesis that substance P contributes to the generation of pain in humans. The reduction in postoperative pain at doses not producing side effects suggests that NK_1 antagonists may be clinically useful. (Clin Pharmacol Ther 1998;64:562-8.)

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The observation by Lembeck[1] of high levels of the 11-amino acid peptide substance P in dorsal spinal roots led to the hypothesis that substance P is a mediator of pain transmission from primary sensory fibers. Substance P is present in 45% of the cell bodies of small afferent neurons that respond to noxious stimuli, often co-localized with glutamate or neurokinin A.[2,3] Substance P most avidly binds to the neurokinin-1 (NK_1) receptor, found on many spinal dorsal horn neurons that respond to noxious stimuli,[4,5] and direct application of substance P onto these neurons produces excitation[6] and hyperalgesia.[3,7,8] In addition to central postsynaptic effects, substance P is released from peripheral nerve endings and may contribute to inflammation and sensitization of peripheral nociceptors by effects such as vasodilatation, increased vascular permeability, and release of inflammatory mediators from leukocytes and mast cells.[9-11]

In contrast to opioid analgesics, NK_1 antagonists have little or no effect on immediate responses to pain in undamaged tissues.[12-15] NK_1 antagonists predominantly reduce behavioral indicators of pain or hyperalgesia preceded by tissue damage or prolonged noxious stimulation.[12-16] In addition to these central actions, NK_1 antagonists also inhibit peripheral inflammatory effects of substance P.[17,18]

CP-99,994, a nonpeptide [(+)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine] selective antagonist

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Supported in part by Intramural Project Grants Z01 DE 00286 NA and Z01 DE 00366 NA from the National Institute of Dental Research, Bethesda, Md, and by Pfizer Central Research, Groton, Conn.
Received for publication Jan 22, 1998; accepted Aug 17, 1998.
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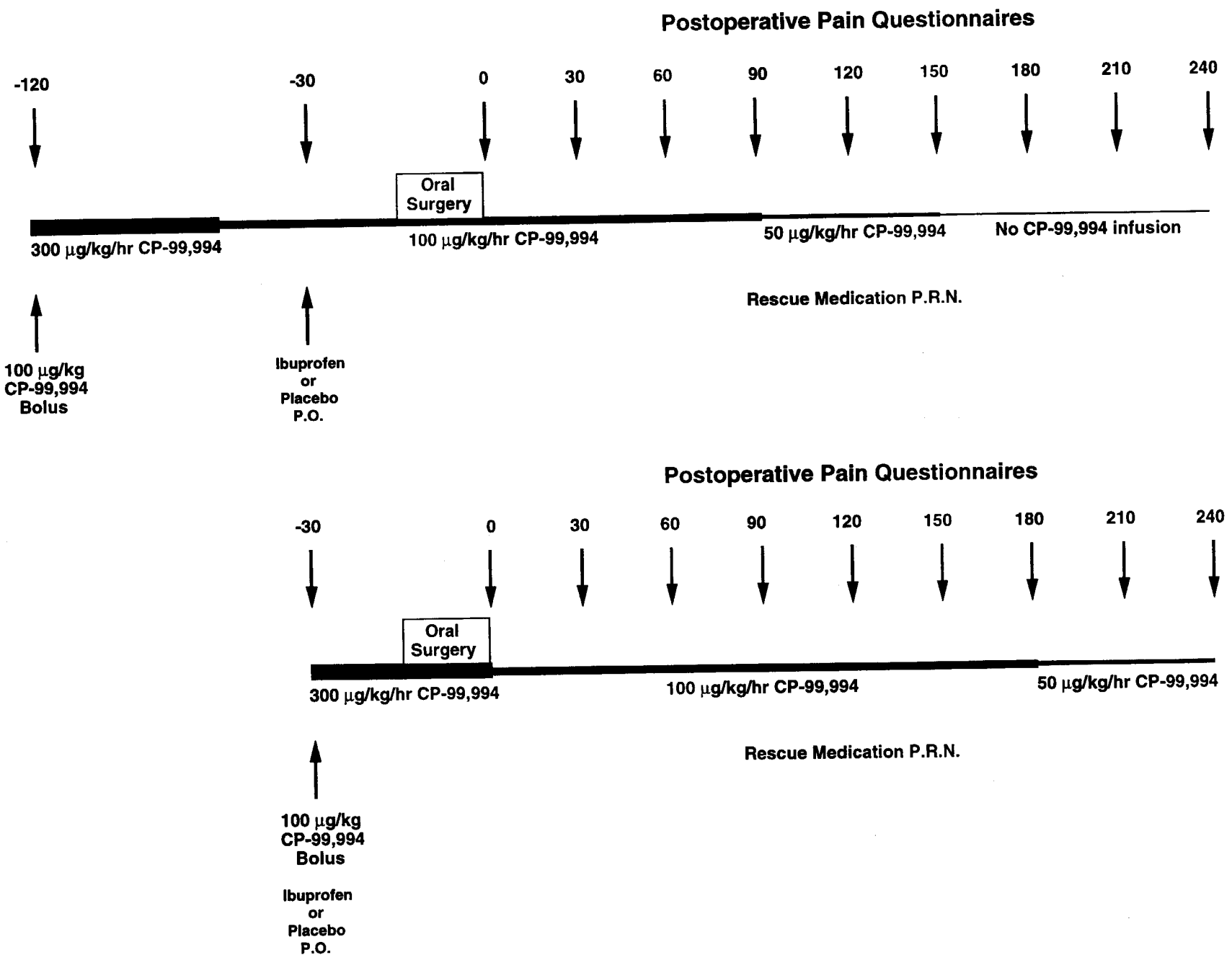

Figure 1. Schematic representation of the CP-99,994 drug infusion schedule relative to the oral surgery, postoperative data collection, and adjunctive drugs administration for both studies.

of the NK_1 receptor, was the first drug in this class to become available for human studies. It readily crosses the blood-brain barrier in animals,[19] binds selectively and with high affinity to NK_1 receptors in a human cell line (dissociation constant [K_d] = 0.4 – 0.6 nmol/L),[19] and produces analgesic effects in animal models.[14,15,20] In both rodents and dogs, the no-observed-adverse-effect level after intravenous administration was 1 mg/kg, nearly 1000-fold greater than those needed to saturate the NK_1 receptor. To assess the effects of NK_1 antagonism on acute inflammatory pain, we conducted 2 double-blind, randomized controlled trials that compared the analgesic activity of preoperative and postoperative intravenous infusion of CP-99,994 to that of preoperative ibuprofen and to placebo.

METHODS

Two clinical trials were conducted sequentially as single-dose, parallel-group double-blind comparisons of CP-99,994 to racemic ibuprofen and placebo in the oral surgery model of acute pain. Patients 18 years or older were eligible to participate if they required the surgical removal of third molars, at least one of which was a partial or full bony impaction, that would normally be expected to produce moderate to severe postoperative pain. Potential subjects were excluded if they had histories of allergic or adverse reactions to any medication or histories of drug abuse or dependence. In addition, subjects were excluded if they had taken an analgesic, anti-inflammatory, or central nervous system depressant drug (with the exception of midazolam used for the procedure) within 48 hours before oral surgery. Female patients of child-bearing potential who were not using oral or depot contraceptives were also excluded. Medical exclusions included a recent history of serious impairment of major organ function, as well as any form of psychiatric illness.

In the first study, intravenous CP-99,994 was administered for 5 hours starting 2 hours before the start of surgery and continuing approximately 2½ hours into

Table I. Summary of demographic characteristics for both studies

	Gender						
	Male	*Female*	*Height (cm)*	*Weight (kg)*	*Midazolam (mg)*	*Lidocaine (mg)*	*Surgical difficulty**
First study							
Placebo	19	1	175.7 ± 1.6	75.3 ± 2.5	5.0 ± 0.4	232.2 ± 10.6	12.1 ± 0.5
CP-99,994	14	5	171.2 ± 2.9	74.3 ± 5.1	5.2 ± 0.2	220.0 ± 11.2	12.7 ± 0.3
Ibuprofen	19	2	172.5 ± 1.6	70.6 ± 2.3	4.9 ± 0.2	237.5 ± 13.4	12.0 ± 0.5
Second study							
Placebo	5	3	170.1 ± 12.8	65.5 ± 11.1	4.4 ± 0.9	191.3 ± 25.3	12.0 ± 2.4
CP-99,994	4	2	174.0 ± 6.3	77.3 ± 11.5	4.2 ± 1.0	214.0 ± 23.0	9.8 ± 1.2
Ibuprofen	2	2	172.0 ± 5.0	64.8 ± 9.6	3.3 ± 0.5	207.0 ± 10.4	10.3 ± 1.7

Data are mean values ± SD.
*Sum of the surgical difficulty for the teeth extracted scored as simple extraction (1), soft tissue impaction (2), partial boney impaction (3), or full boney impaction (4).

the postoperative period (Figure 1). A bolus of 100 μg/kg was infused initially over the first 6 minutes, followed by 300 μg/kg over the first hour, then 100 μg/kg/hour for the next 3 hours, and finally 50 μg/kg over the final hour, for a total dose of 750 μg/kg. In the second study, the same dose regimen was shifted to begin 30 minutes before the start of surgery and continued during surgery and approximately 4 hours into the postoperative observation period. In phase I studies in normal volunteers, this infusion regimen resulted in plasma concentrations of 40 to 120 ng/mL over the first 2 hours. Such concentrations were associated with a minimum 16-fold increase in the cumulative dose of substance P that caused an increase in cutaneous blood flow and a decrease in blood pressure (S.C. Harris, D.B. MacLean, J. Venity, unpublished observations, December 1997). A single blood sample was collected in both studies for measurement of CP-99,994. Ibuprofen levels were not measured because the time course of this prototypic drug has been well characterized.

The ibuprofen and placebo control groups received intravenous saline solution according to the CP-99,994 schedule. The ibuprofen group received a single dose of 600 mg ibuprofen administered orally 30 minutes before surgery in both studies, and the CP-99,994 and placebo groups received matching placebo capsules (double-dummy design). Administration of ibuprofen 30 to 60 minutes before oral surgery suppresses pain in the immediate postoperative period,[21,22] providing a positive control for analgesic activity in comparison to placebo.

The oral surgery procedure was performed with intravenous midazolam premedication and 2% lidocaine with 1:100,000 epinephrine used for local anesthesia. A mucoperiosteal flap was raised and retracted, bone was removed, and the teeth were sectioned as needed to facilitate extraction. Sutures were placed, a gauze was placed over each extraction site, and patients were moved to the recovery room for observation and postoperative data collection.

Analgesic questionnaires were completed by the subjects every 30 minutes for 240 minutes after surgery. The presence of residual local anesthesia was assessed at each time point by having patients tap on each side of the lower lip and score the sensation as "normal," "tingling," or "numb." Subjects were excluded from analysis if numbness persisted bilaterally at 180 minutes. Pain intensity was recorded with a category scale scored as none (0), mild (1), moderate (2), or severe (3). A 100-mm visual analog scale (VAS) for pain intensity was also completed at each observation with a left end point of "none" and a right end point of "worst possible pain." Figure 1 summarizes the time line for the treatments and data collection in the 2 studies.

The VAS estimates of pain intensity were analyzed at each postoperative time point by 1-way ANOVA with post hoc Duncan's multiple range test. Pain intensity as measured by the category scale and the categorical estimates of residual local anesthesia were analyzed by the nonparametric Kruskal-Wallis test with post hoc multiple comparisons. The incidence of adverse effects was evaluated by χ^2 analysis.

RESULTS

A total of 60 subjects completed the first study and were similar across groups in the distribution of sex, mean weight and height, doses of midazolam and lidocaine, the offset of local anesthesia, and the sum of the surgical difficulty scores for the extractions (Table I). Pain intensity, as measured by VAS, increased coincident with the waning of anesthesia in the placebo-treated group to reach a mean pain intensity of approximately 70 mm at the last 3 observations (Figure 2, *upper panel*). Preoperative administration of ibuprofen resulted in significantly less pain than placebo from 90

to 240 minutes after surgery, and in comparison to CP-99,994 from 120 to 240 minutes. Pain intensity was significantly less than placebo in subjects receiving CP-99,994 only at 90 minutes after surgery.

Pain as measured by category scale increased in the placebo group to reach a mean value equivalent to "moderate" over the last 120 minutes of the observation period (Table II). Ibuprofen significantly suppressed pain in comparison to placebo from 60 to 240 minutes, and in comparison to CP-99,994 from 120 to 240 minutes. No significant difference between CP-99,994 and placebo was detected by category scale.

Only 18 subjects completed the second study because of the expiration of the investigational drug supply. The distribution of sex, mean weight and height, doses of midazolam and lidocaine, the offset of local anesthesia, and the sum of the surgical difficulty scores for the extractions were similar across groups (Table I). Both CP-99,994 and ibuprofen suppressed pain as measured by VAS in comparison to placebo at 60 to 120 minutes after surgery but did not differ significantly from each other (Figure 2, *lower panel*). The results of the category scale were similar, although nonsignificant, at all but 1 time point, presumably because of the small sample size (Table II).

The incidence of adverse effects reported in both studies were combined because the doses of ibuprofen and CP-99,994 were unchanged between studies. The number of patients not reporting any adverse effects, as well as the type reported, were similar across treatment groups (Table III).

Blood samples obtained at 90 minutes after the start of drug infusion from 18 of the 19 subjects receiving CP-99,994 in the first study resulted in measurable serum concentrations in all samples, with a mean of 89.5 ng/mL (range, 48.1 to 134.0). Blood samples collected in the second study at 180 minutes from the start of the infusion were much lower, with a mean of 11.5 ng/mL (<0.1 to 53.1), reflecting the rapid elimination of the drug as the infusion rate was lowered.

DISCUSSION

The results of this clinical study provide the first human data to support the hypothesis that substance P is involved in the generation of pain in humans and to show that the nonpeptide antagonist CP-99,994 relieves pain at doses that do not appear to cause significant side effects. In both studies, significant pain relief was observed only while the CP-99,994 was being infused at a rate of 100 μg/kg/h or greater. This suggests that the analgesic effect of CP-99,994 is rapidly reversible after plasma levels decline.

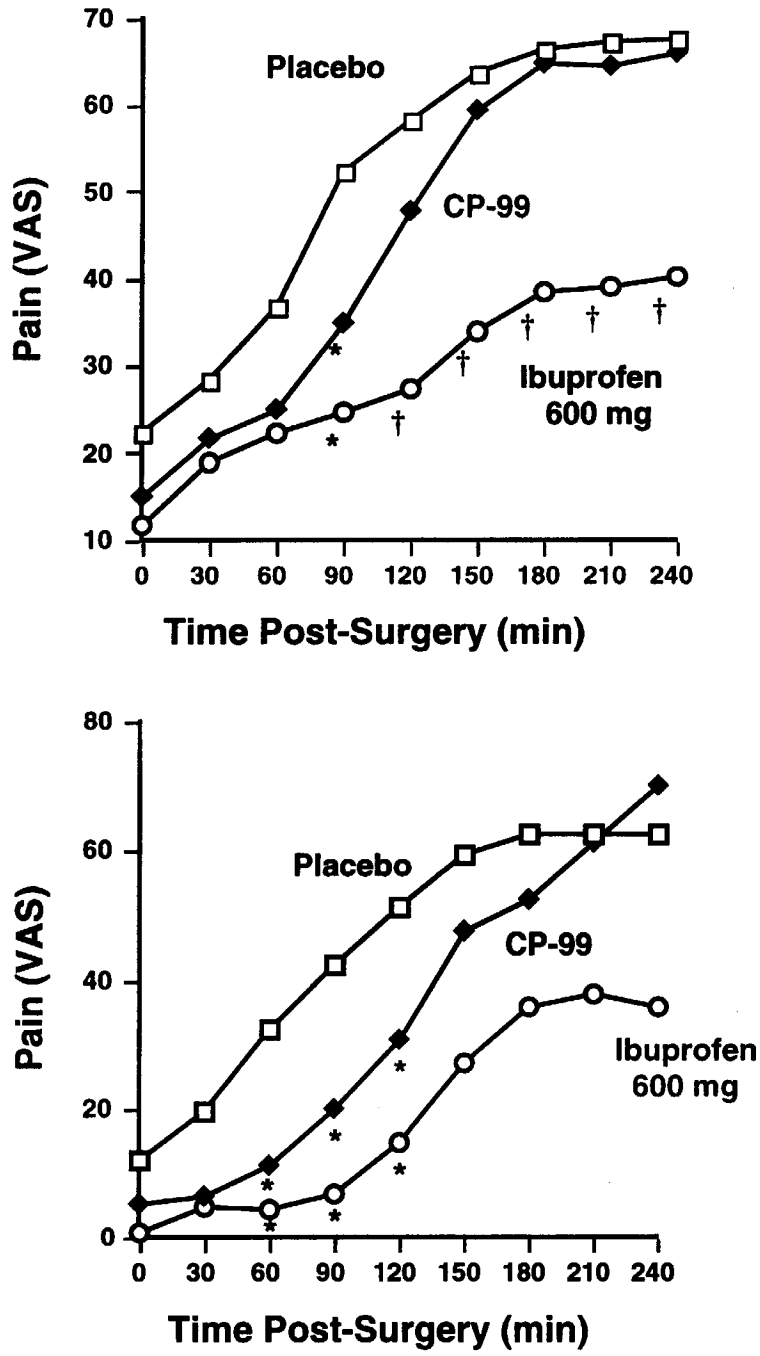

Figure 2. Pain intensity scores for both studies as measured by visual analog scale (VAS) after the end of surgery (time 0) for the 3 treatment groups. **Upper panel,** First study: $*P < 0.01$ versus placebo; $\dagger P < 0.05$ versus placebo and CP-99. **Lower panel,** Second study: $*P < 0.05$ versus placebo.

In both of the studies, the peak analgesic effect of CP-99,994 was approximately half that of pretreatment with 600 mg ibuprofen. The oral surgery model is very sensitive to the effects of nonsteroidal anti-inflammatory drugs,[23,24] with normal oral doses of ibuprofen and flurbiprofen, for example, displaying greater analgesic activity than opioid combinations such as acetaminophen (INN, paracetamol) plus codeine or acetaminophen plus oxycodone. The reduction in pain with CP-99,994 relative to ibuprofen might have been greater with a higher dose, a more prolonged infusion, or use of a different NK_1 antagonist with a longer duration or greater intrinsic activity. The observation that CP-99,994 produced an incidence of adverse effects similar to placebo in this study suggests that higher doses might have been used, with the potential for demonstrating greater analgesic efficacy.

Table II. Subjective estimates of pain intensity post-surgery (min) by the category scale

	0 min	*30 min*	*60 min*	*90 min*	*120 min*	*150 min*	*180 min*	*210 min*	*240 min*
First study									
Placebo	0.7 ± 0.7	0.8 ± 0.7	1.2 ± 0.6	1.7 ± 0.8	2.0 ± 0.8	2.2 ± 0.7	2.3 ± 0.7	2.3 ± 0.6	2.3 ± 0.6
CP-99,994	0.5 ± 0.6	0.5 ± 0.6	0.7 ± 0.7	1.1 ± 0.9	1.6 ± 0.8	2.0 ± 0.7	2.2 ± 0.7	2.2 ± 0.7	2.2 ± 0.6
Ibuprofen	0.5 ± 0.6	0.6 ± 0.7	0.6 ± 0.7*	0.8 ± 0.8*	0.8 ± 0.7*†	1.1 ± 0.9*†	1.4 ± 0.8*†	1.5 ± 0.8*†	1.4 ± 0.8*†
Second study									
Placebo	0.5 ± 0.5	0.8 ± 0.4	1.4 ± 0.5	1.4 ± 0.7	1.8 ± 0.5	2.0 ± 0.0	2.2 ± 0.6	2.2 ± 0.4	2.2 ± 0.4
CP-99,994	0.2 ± 0.4	0.3 ± 0.5	0.5 ± 0.8	0.7 ± 0.8	1.2 ± 0.8	1.3 ± 0.8	1.8 ± 0.8	2.2 ± 0.8	2.3 ± 0.5
Ibuprofen	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5	0.8 ± 1.0	1.3 ± 0.5	1.3 ± 0.5*	1.5 ± 0.6	1.5 ± 1.0

Data are mean values ± 1 SD.
*$P < 0.05$, ibuprofen versus placebo.
†$P < 0.05$, ibuprofen versus CP-99,994.

Table III. Incidence of adverse effects for both studies combined

	None	*Syncope*	*Nausea*	*Headache*	*Dizziness*	*Other*
Placebo	24/28	1	1	1	0	1
CP-99,994	20/25	0	1	1	0	3
Ibuprofen	23/25	0	2	0	1	3

Another possible reason for observing relatively modest effects of a specific NK_1 antagonist may be that many neurotransmitters, in addition to substance P, contribute to the generation of pain, including glutamate,[25,26] neurokinin A,[3,27] and adenosine triphosphate.[28] This explanation is supported by animal studies indicating that intrathecal administration of NK_1 antagonists rarely yields more than 50% to 80% inhibition of hyperalgesia in various models of paw inflammation,[14,29,30] and analgesia diminishes or disappears if larger doses of the proinflammatory substance are used.[14]

A further explanation for the modest analgesic effect of CP-99,994 given immediately before and after surgery is that substance P may not become a major contributor to pain until many hours or days after an injury. NK_1 receptor antagonists produce little or no antinociceptive effect in electrophysiologic[31] or behavioral assays involving uninjured tissues[12-15] but substantial effects after prolonged noxious or inflammatory stimuli.[12-15,27] More slowly activated mechanisms may also be involved. For example, the number of NK_1 receptors in the spinal dorsal horn increases 1 day after injection of complete Freund's adjuvant into the paw and 3 days after sciatic nerve section.[32] Local inflammation also produces an increase in substance P content of spinal nerves and dorsal horn,[33,34] in part by causing myelinated primary sensory neurons that normally mediate light touch to begin producing substance P.[2] This phenotypic switch, mediated partly by nerve growth factor, reaches a maximum at 48 hours,[35] the time at which clinical manifestations of surgically induced inflammation also reach a peak.[22] NK_1 antagonists may result in greater analgesia than shown in this study if administered during later phases of postoperative inflammation, in chronic inflammatory conditions such as arthritis and degenerative spinal disc disease, or in fibromyalgia, a syndrome in which elevated levels of cerebrospinal substance P have been reported.[36,37]

An alternative explanation for the modest analgesic effect of CP-99,994 observed in this study is that although substance P may be a powerful mediator of pain sensation at some synapses, pain-inhibiting effects at other synapses may cause the net effect of NK_1 receptor blockade to be small. Animal experiments have suggested a number of possible mechanisms whereby substance P may activate endogenous analgesic processes in the brainstem[19,38,39] and spinal cord.[30,40,41]

The nociceptive effects of the substance P–NK_1 receptor interaction appear to enhance the action of other nociceptive mechanisms, such as the *N*-methyl-D-aspartate glutamate receptor system,[42,43] raising the possibility that combinations of antagonists will be useful. Because the analgesic effects of treatment with currently available *N*-methyl-D-aspartate glutamate receptor antagonists are limited by dissociative side effects,[44,45] NK_1 receptor blockade may be a less toxic indirect method of reducing *N*-methyl-D-aspartate glutamate receptor activation. Combinations of NK_1 antagonists with NK_2 or *N*-methyl-D-aspartate glutamate receptor antagonists or other analgesic drugs, such as non-

steroidal anti-inflammatory drugs, opioids, or α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid–kainate receptor antagonists may therefore allow greater levels of analgesia at tolerable doses. The opportunities offered by the NK_1 antagonists and other new analgesic candidates should stimulate the systematic investigation of analgesic combinations and help to elucidate the predictive value of animal and human pain models for efficacy in particular clinical pain syndromes.

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